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The new regulation to investigate potentially beneficial diagnostic and therapeutic methods in Germany: Up to international standard?☆



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ABSTRACT

Funding of diagnostic and therapeutic methods in Germany's statutory health insurance (SHI) follows a dichotomy: in outpatient care, only methods with proven benefit are reimbursed while in inpatient care, all methods may be provided unless they are excluded due to proven harm or lack of benefit. In January 2012, a new section 137e was added to the Social Code Book V (SGB V), allowing for the inclusion of innovative and potentially beneficial diagnostic or therapeutic methods in the SHI benefit basket, while additional evidence regarding their effectiveness and safety must be gathered. In 2013, the Federal Joint Committee (G-BA) has specified the details of this new approach, which can be considered a variety of "Coverage with Evidence Development" (CED). Our comparison with CED schemes in selected countries reveals a dependence of the CED implementation on the encompassing healthcare system. However, we identify a clear legislative foundation, a definitive decision-making body, the possibility to obtain public funding, and the preference for high quality study designs as constituting factors of an emerging international standard for CED. In addition, it is necessary to ensure the suitability of circumstances and technologies for the successful application of CED in a clear and transparent way.

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1. Introduction

The principles of evidence-based medicine (EBM) have become standard for all levels of healthcare decision-making [1]. However the EBM approach has shortcomings

in the adoption of promising technologies that are potentially beneficial for patients, highly cost-effective or even cost-saving, but for which the quality of evidence is insufficient to justify full coverage [2]. One common approach that has been used in resolving this dilemma is health technology assessment (HTA). HTA has been widely adopted to support decision-making regarding the introduction and adequate use of new technologies. Nevertheless, the majority of HTA activities have been limited to pharmaceuticals. Other interventions – also called 'methods' – such as new medical devices or procedures (surgical and non-surgical) have less often, or never, been assessed by HTA before implementation [3]. Dealing with the shortcomings of EBM and HTA as well as the increasing pressures on health

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care budgets of costly innovative treatment options, policy makers and key stakeholders have begun to invest in new approaches to initiate and use clinical research [2,4].

One option within this context is the coverage with evidence development (CED) approach. CED represents a specific policy tool, providing provisional access to novel medical interventions while the evidence needed to assess the value of an intervention and consequently to make coverage unconditional is generated [5]. Thereby it addresses the needs of different stakeholders such as decision makers, manufacturers, patients, and health service providers [3,6]. For example, CED offers an option for government bodies to make a technology available in a controlled manner while in addition allowing them to predetermine which evidence will be needed to ensure further use and coverage of the technology. From the manufacturers' perspective (e.g. medical device companies), CED gives the opportunity to introduce a new and promising technology which otherwise might be rejected. Last but not least, CED might be relevant for healthcare providers and the patients, because it provides earlier accessibility to promising technologies and consequently a broader range of available treatment options [3]. CED – in some way or form – has already been implemented in many countries throughout the world (e.g. Australia, United Kingdom (UK), France, The Netherlands or Canada), usually as part of an established policy framework [7]. In consequence, it is known under various terms such as 'interim funding' [8], 'only in research (OIR)' [9], 'still in clinical research' [10], and 'conditionally funded field evaluation (CFFE)' [11]. However, the term CED has been coined by the Centers for Medicare & Medicaid Services (CMS) in the United States (US), which published guidelines regarding the relevance and use of CED in 2005. Further revisions followed in 2006 and most recently in 2012/2013 [12]. Increasingly, attempts are being made to further develop or expand such CED mechanisms and tailor them to countries' specific health care systems [5,6]. One recent example is the new regulation in Germany. In January 2012, a new section 137e has been added to the German Social Code Book V (SGB V). It can also be seen as a further scheme within the scope of CED approaches. While plenty of literature on the varying established CED schemes exists, little or no description and analysis of this new legislation in Germany has been conducted so far [5,7,9,11,13]. Additionally, the introduction of yet another CED scheme prompts the question whether a standard in CED is emerging.

Therefore our primary goal in this study is to give a more detailed understanding of the new German regulations regarding section 137e SGB V as a further variation of the CED approach. As the new regulation does not concern pharmaceuticals, this manuscript focuses only on diagnostic and therapeutic methods. It gives insight into the motives for implementing this new regulation, the relevant specifics, the general evaluation procedure, followed by a description of the consequences for the in- and outpatient care setting, and an outlook regarding the impact of the new regulation. We will further compare the new German regulation to other representative examples of CED directives in an outside Europe in order to answer the question whether an international standard is emerging.

2. The regulation of diagnostic and therapeutic methods in the in- and outpatient care setting in place prior to the reform

In Germany's statutory health insurance (SHI) system, newly licensed pharmaceuticals and diagnostic or therapeutic methods are regulated in different ways. However, both are regulated by the same decision-making body, the Federal Joint Committee (G-BA). The G-BA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals, patients and health insurance funds in Germany. It issues directives for the benefit basket of the statutory health insurance funds for more than 70 million insured individuals and thus specifies which services in medical care are reimbursed by the SHI. In addition, the G-BA specifies measures for quality assurance in inpatient and outpatient areas of the health care system [14]. As mentioned in the beginning, this article will focus only on diagnostic and therapeutic methods. An up-to-date analysis of recent changes regarding the regulation of pharmaceuticals in Germany can be found in Henschke et al. [15].

According to the Federal Social Court (e.g. case no. B 1 KR 10/09 R) a diagnostic or therapeutic method is generally defined as a medical procedure embedded in a treatment plan under a physician's care, based on a specific theoretical and scientific concept. It involves several steps usually involving medical devices differentiating it from other (one-step) procedures and thus justifying its systematic application in the examination and treatment of specific diseases [16]. This understanding of a method comprises a broad spectrum of new diagnostic and therapeutic methods and entails a broader concept than the application of medical devices alone, such as medical aids. However, not every new non-pharmaceutical treatment can be seen as a method [17]. For example, if a patient takes daily blood pressure measurements to monitor her blood pressure levels herself, this does not yet constitute a method. If, however, the blood pressure measurements are part of a Disease Management Programme (DMP) and are being transmitted to the patient's doctor in order to facilitate treatment adjustments, they do constitute a method.

So far, diagnostic and therapeutic methods in the in- and outpatient sector only come under consideration by the G-BA when a stakeholder organisation – this includes the impartial members of the G-BA, the regional associations of SHI physicians, the federal association of SHI physicians (KBV), the federal association of statutory health insurance funds (GKV-SV), or the patient representatives in the G-BA – applies for a benefit assessment. This is usually the case when there is uncertainty regarding the patients' benefit of a method. There are two different existing routes to inclusion of diagnostic and therapeutic methods into the benefit basket in Germany:

- (1) Methods intended for use in the outpatient care setting are regulated by section 135 of the SGB V. The regulation includes a so-called *prohibition rule with the reservation of permission*. Under this rule, new diagnostic and therapeutic methods are only added to the

benefit basket if the G-BA comes to a positive decision regarding these methods [18]. A positive decision will only be achieved if the benefit of a new method has been proven by sufficient evidence based on available studies. In addition, based on section 12 (subsection 1) SGB V, the method has to be medically necessary and economically efficient [18]. Positively evaluated methods are added to the Physicians' or Dentists' Uniform Value Scale (*Einheitlicher Bewertungsmaßstab* or *Einheitlicher Bewertungsmaßstab für zahnärztliche Leistungen*), which list reimbursable services and thus also serve as benefit catalogues for the respective sectors [19].

- (2) In contrast, in the inpatient care setting, section 137c SGB V defines the principle of *permission unless explicitly banned*. This means that all methods – including new ones – can be used without any acknowledgement of benefit as long as the G-BA does not explicitly ban a method based on the available evidence. Most established methods are included in the cost calculation of the German Diagnosis-Related Group (DRG) system and thus in the DRG payments or supplementary payments by the sickness funds [20]. New diagnostic and therapeutic methods may qualify for extra-budgetary “NUB” (new examination and treatment methods) payments if (1) they are more expensive than the one included in the calculation of an existing DRG and if (2) a funding agreement has been reached between sickness funds and hospitals on a local level [21].

As the description of the two routes regarding the implementation of new diagnostic and therapeutic methods into the benefit basket illustrates, the G-BA has the legislative tools to exclude methods because of proven harm or a lack of evidence for patient benefit, but no valid options to request the generation of evidence [22].

3. The coverage with evidence development reform—New section 137e SGB V

The G-BA evaluates the benefits of treatment methods by applying the criteria of EBM [1]. After a systematic search for the best available evidence on the topic of interest, results are evaluated with respect to their validity, plausibility and applicability. Under the principles of EBM, methods would not be excluded due to a lack of positive demonstration of an added benefit, as it would be inadequate to infer a lack of benefit from missing evidence [22,23]. The G-BA therefore needs a mechanism for inducing the generation of scientific evidence for decision-making in the EBM framework. Such a mechanism is provided by section 137e SGB V.

3.1. Motives for implementation

Criticism had been raised particularly regarding the regulations in the inpatient care setting. As new diagnostic and therapeutic methods do not have to undergo a structured assessment under section 137c before being provided in hospitals, the patient-benefit (or possible risk) often

remains uncertain for the patient, mainly due to the lack of evidence from high quality studies.

Experiences with lengthy and controversial decisions regarding the exclusion of methods by the G-BA have shown that the conditions for the generation of knowledge that are needed for decision making must be improved [24]. One example is positron emission tomography (PET) for different indications, which has been under consideration since 1998. The G-BA could only form a decision on five indications and excluded PET for three (partly in two of the three cases) of them. For two other indications (colorectal and esophageal cancer) the decision-making process was suspended due to remaining uncertainties about the evidence and coinciding signs for being a valid treatment alternative. About ten more indications are currently under consideration.

In addition, no information about the number of methods implemented in the clinical care setting without proven evidence is available [22]. Only since the year 2000, some of the most controversial diagnostic and therapeutic methods have been brought to consideration by the G-BA and a number of them have been excluded due to lack of evidence or because of an unfavourable benefit–risk assessment. Table 1 aims at giving an overview of currently excluded hospital treatment methods. At the moment (only) 15 methods in the inpatient care setting are excluded by the G-BA based on the lack of evidence for patient benefit [25].

3.2. Specifics of the new stipulation

With the introduction of the new section 137e SGB V through the SHI Care Structures Act (GKV-VStG) in January 2012, a new legal tool has been created to prospectively test innovative diagnostic and therapeutic methods that have the potential to be viable alternative to the current standard under structured conditions. A diagnostic and therapeutic method is defined as *new* if:

- it is not listed in relevant documents like the Physicians' or Dentists' Uniform Value Scale or
- it is listed in the Physicians' or Dentists' Uniform Value Scale, but shows substantial changes regarding its indication or how it is delivered, and
- the method under evaluation falls within the scope of statutory health insurance in Germany, as stated in the second chapter, section 2 of the rules of procedure of the G-BA (*Verfahrensordnung*) [26].

The new stipulation has a sound legal basis (SGB V), which is legitimised by the German Parliament, and complements the regulations under sections 135 and 137c. All details regarding the trial procedures in accordance with section 137e SGB V are defined in the G-BA's rule of procedure [26].

A key element when assessing a new method under section 137e SGB V is that it needs to show *potential* for additional patient-relevant benefit in comparison to a current standard or benchmark method. The G-BA delegates the evaluation of new candidate methods regarding their potential for improvement to the Institute for Quality and Efficiency in Health Care (IQWiG). In general,

Table 1

Excluded inpatient treatment methods (in chronological order of initial decision).

Excluded diagnostic and therapeutic methods—inpatient care setting (section 137c)	Year of decision
Autologous chondrocyte implantation (ACI); in 4 indications	2003: 2 indications; 2009: 1 indication; 2010: 1 indication
Hyperbaric oxygen therapy (HBOT); in 8 indications	2003: 2 indications; 2004: 3 indications; 2008: 1 indication; 2009: 2 indications
Proton beam therapy; in 10 indications	2003: 3 indications; 2007: 1 indication; 2009: 3 indications; 2010: 2 indications; 2011: 1 indication
Positron emission tomography (PET; PET/CT); in 3 indications	2008: 2 indications; 2011: 1 indication
Both hybrid-laser-treatments potassium-titanyl-phosphate/neodymium yttrium aluminium garnet (KTP/Nd:YAG) and contact-laser-ablation/visual laser-ablation (CLAP/VLAP) for the treatment of benign prostatic syndrome (BPS)	2010
Interstitial laser coagulation (ILK) for the treatment of benign prostatic syndrome (BPS)	2010
Holmium-laser ablation (HoLAP) for the treatment of benign prostatic syndrome (BPS)	2010
Holmium-laser bladder neck incision (HoBNI) for the treatment of benign prostatic syndrome (BPS)	2010
Transurethral radiofrequency needle ablation (TUNA) for the treatment of benign prostatic syndrome (BPS)	2010
High intensity focused ultrasound (HIFU) for the treatment of benign prostatic syndrome (BPS)	2010
Water induced thermotherapy (WIT) for the treatment of benign prostatic syndrome (BPS)	2010
Transurethral ethanol ablation (TEAP) for the treatment of benign prostatic syndrome (BPS)	2010
Thulium-laser ablation (TmLAP) for the treatment of benign prostatic syndrome (BPS)	2011
Autologous stem cell transplantation for the treatment of acute lymphoblastic leukemia (ALL) in adults	2011
Exclusive use of antibody-coated stents for the treatment of coronary vessel stenosis	2013

Source: [25] (in German).

demonstrating that a new diagnostic and therapeutic method is not being harmful or ineffective is not enough to fulfil the underlying concept of potential. To show potential, the method rather needs to demonstrate potential based on the mechanism of action and the evidence available so far. In particular, this means it should be more effective, less complicated, less invasive, or less harmful or able to replace less efficacious methods in specific groups of patients. The method may be an optimisation of an existing treatment, or otherwise lead to an improvement in the medical treatment. [27]. It is also crucial in this context that the scientific documents submitted by the applicant are sufficient to serve as a basis for clinical study planning in order to assess a new method's benefit with sufficient certainty. However, the key items of the trial phase, such as indication, study population, intervention, study design, appropriate comparator, outcomes, study duration, practical/staff, and other quality requirements necessary to specify the research question, are determined by the G-BA in accordance with chapter two (section 22), of the rules of procedure. Applicants have the opportunity to issue their

views in a comments procedure before a clinical trial is commissioned [26].

The specifics regarding costs of the trial phase and their reimbursement are defined in the G-BA's schedule of costs [28]. Generally, costs during the assessment phase for the service provision itself will be covered by the sickness funds [18,28]. Manufacturers only have to pay for overhead costs of the clinical trial if a medical device is essential for the new method. These overhead costs include costs for the preparation of a study protocol, the scientific monitoring and the evaluation of the study results, which are all performed by an independent scientific institute [18,26].

3.3. Procedures and decision-making under the new stipulation

Until now, only the stakeholder organisations and the impartial members, as given above, have been allowed to submit requests calling for an assessment of new or already established and reimbursed diagnostic or therapeutic methods to the G-BA (see section 2). According to

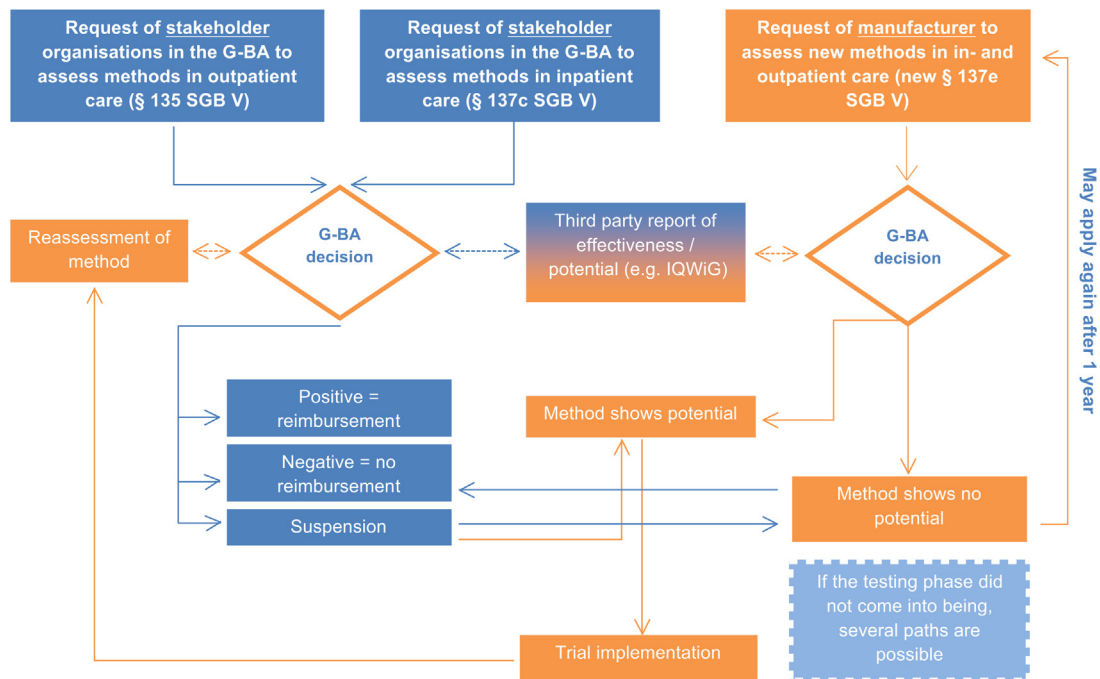


Fig. 1. The decision-making process of methods in the in- and outpatient care setting (simplified overview) [29].

the revised rules of procedure, for the first time, manufacturers of medical devices, and other companies that have an economic interest in their provision, are granted to specifically apply for the testing of new diagnostic and therapeutic methods under the new section 137e SGB V [18]. Applications may also be submitted for methods not requiring a medical device (e.g. manual therapy or psychotherapy). Fig. 1 gives a simplified representation of the three coexisting decision-making processes regarding new and already established diagnostic and therapeutic treatment methods in the in- and outpatient care setting [29].

On the basis of such a request for assessment by the manufacturer, the G-BA commissions the IQWiG to evaluate the potential of the new method. In case, the G-BA – on the basis of the IQWiG's results – assesses the method as showing potential and decides to conduct a trial, it develops and publishes a directive that defines a trial phase for the method in question and commissions an independent scientific institute to plan and conduct the evaluation [26]. Such a trial phase only exists under the new section 137e SGB V.

Once the trial phase is completed, the G-BA re-evaluates the trial data and makes a final decision whether the method is approved or rejected. There is no predefined time frame for this reassessment. Should the trial results demonstrate an additional patient benefit, the G-BA approves the new method as reimbursable in the in- and outpatient sector. Conversely, if – under the new stipulation – the new method shows no potential or the clinical data gathered during the trial phase does not show that the new method serves as a valid treatment alternative, the G-BA publishes a directive in which the new method is added to the 'exclusion list' (Annex II of the Guidelines

on SHI accredited outpatient methods, as seen in Table 1). Methods listed in Annex II are not reimbursed by the sickness funds [18]. In some cases the testing phase may not come into being even if the method displays potential (e.g. because a manufacturer refuses to pay for the overhead costs). However, unless a method was evaluated in a clinical trial and afterwards added to the 'exclusion list', manufacturers may apply for reassessment after a waiting period of one year (see Fig. 1).

3.4. Consequences for the in- and outpatient care setting

Due to the different reimbursement rules in German ambulatory and inpatient care, the new regulation may impact these two sectors differently.

First, it offers a chance for new methods in the outpatient care setting to transform the *prohibition rule with the reservation of permission* (according to section 135 SGB V) into a conditional permission until a final decision has been reached based on the gathered clinical data during the trial phase [30].

Second, prior to the new regulation, there were three possible outcomes for methods assessed regarding the inpatient care setting (see Fig. 1): (i) confirmation of patient-relevant benefit, (ii) exclusion of the method because of lack of evidence or evidence for harm and (iii) suspension of the consideration because of lack of evidence. While exclusion of the method refers to an immediate exclusion from any insurance reimbursement, suspension of the consideration does not. In the latter case, the method is being reimbursed for a temporary period, while new evidence may be gathered. In some cases, the G-BA might have suggested a specific study design, but there was no

possibility for the G-BA to enforce the generation of evidence. Under the new stipulation – in case of insufficient evidence – the assessment is suspended as under the previous legislation but a clinical trial *has to be* initiated, if the method shows potential to be beneficial. Exclusion under section 137e, is only possible if the results of the initiated trial show lack of benefit or even harm or if the trial does not come into being [18]. In addition, diagnostic and therapeutic methods that are suspended under section 137c due to uncertainties regarding the evidence but show potential and trial registries do not indicate one or more relevant studies to be published soon, now have to come under consideration through section 137e (see Fig. 1).

3.5. Outlook

The G-BA has amended its rules of procedure in order to translate the legal mandate into a manageable process. This amendment has been published in June 2013 in the Federal Gazette [31]. Currently, only one assessment under the new regulation has been initiated (PET in the indication for colorectal cancer). Over the coming years, more decisions on new methods will follow. However, the type and exact number of methods is not clear yet. It is expected that applications with regard to the new CED pathway will mainly concern the outpatient sector, since new methods require G-BA approval. Nevertheless, applications may also be filed for conducting studies in the hospital sector, despite explicit approval by the G-BA being unnecessary.

In addition it is anticipated that companies will seek advice regarding the formalities of the application process, methodological requirements for the assessment, suitability of a new method for consideration under section 137e SGB V, and funding specifics. The G-BA office will provide such advice in co-operation with a dedicated working group of the G-BA [26].

4. Discussion and international comparison

Having described the details of the new German legislation, we now discuss its possible advantages and disadvantages. The main improvement of section 137e SGB V is that it allows for new and potentially beneficial methods in the inpatient care setting to be scheduled for trial before exclusion from coverage, if these methods lack evidence regarding their effectiveness and safety. In addition in the outpatient care setting, physicians and patients may get access to new and promising treatment options earlier. The approach is innovation-friendly and attractive for manufacturers mainly in the outpatient sector, since they are able to conduct studies that are financially supported by the sickness funds (payment for the service provision). In addition, the legislation is expected to reduce the duration of the G-BA's consultation procedures, because it facilitates the decision by the G-BA's stakeholders in cases lacking sufficient evidence. Although the new stipulation is a useful development with respect to the assessment of new and promising methods, it also suffers from several limitations worth considering: under the legislation, exclusion of a new method in the absence of evidence is no longer possible in the inpatient setting, as the G-BAs' assessment

needs to show that the method is either less effective than the standard treatment or harmful. If a method is proven to be less effective or even harmful after finalisation of a CED trial, it has to be delisted from the benefit catalogue, although controversies will be likely. This applies to the inpatient sector, since some of these methods might have been part of routine care since decades.

Furthermore, when the G-BA initiates a study, the new method can also be applied in the inpatient setting outside the trial, which may lead to difficulties in patient recruitment. Therefore, it is to be expected that the German CED approach is less attractive for setting up studies in the inpatient sector. In addition, due to the lack of proven benefit, the risk for the patient to be exposed to potentially ineffective or even harmful treatment methods during the evaluation is not mitigated. From the perspective of the SHI system, patients are exposed to potentially ineffective and expensive methods during the evidence development phase. Furthermore, it will be challenging to draw a line between sufficient evidence for demonstration of the potential and the evidence necessary for planning a study (e.g. a RCT) [26,27]. Finally, issues that need to be addressed in the future remain. The G-BA has no ability to rule out the 'free-rider phenomenon', i.e. a company with an innovative device pays for a clinical trial and another competing company launches its product after the (successful) evaluation and thus benefits from the pioneering company's investment. The procedure is still time-consuming. On average it takes 30 months, excluding the duration of the trial. A priority-setting process has not been established yet since it is not clear how many applications will be filed. This could become a matter of critique in the future, when the number of methods with a potential for additional patient benefit will exceed the capacity of the G-BA to manage them.

The new stipulation in Germany adds to the mix of already implemented CED schemes in- and outside Europe. Therefore it is only logical to ask how well the new German approach fares in comparison to other implementations of CED internationally. Moreover we are interested in investigating whether an international standard for CED is emerging. To achieve this we provide information about key political, structural and methodological attributes of different CED schemes from selected countries in Table 2.

The respective countries are chosen as representative examples of different Western health care systems ranging from single-payer schemes to social insurance models. We do not intend to give a complete review of existing international approaches. Our data mainly stem from information available in the public domain (e.g. governmental and related organisations' webpages). Where necessary we fill the gaps with data available in the literature or information obtained directly from the individuals involved in the decision process regarding conditional reimbursement of new diagnostic and therapeutic methods in a given country (e.g. inside the relevant institution or organisation).

The comparison shows that the German implementation of CED does, indeed, have features in common with its international counterparts. However, there are still differences with respect to the schemes' structures,

Table 2

Comparative overview of key attributes across CED schemes (as of April 2014; in alphabetical order).

Attributes	Australia	Canada (Ontario)	France	Germany	The Netherlands	UK (England/Wales)	USA
Name of the CED system	Interim funding	Conditionally funded field evaluation	Still in clinical research	Evaluation of new diagnostic and therapeutic methods	Conditional entry into the basic package ^a	Only in research	Coverage with evidence development
(Legal) basis	Health Insurance Act (1973)	Administration/delivery of healthcare services is each province's/territory's responsibility based on the Canada Health Act ^b	Article L.165-1-1 of the French health social security code ('Forfait innovation')	Section 137e of the Social Code Book Five (SGB V)	As of 1 January 2012 rooted in the health care law	MTG/DG is advisory; IPG can limit use of interventional surgical/other procedures if limited evidence for safety and/or efficacy is limited	Section 1862 (a)(1)(A) of the Social Security Act, called the "reasonable and necessary" statute
Funding	Mainly public (department of Health and Aging)	Public (by MOHLTC)	Mainly private (manufacturers); HAS is not involved in the choice of financing modality	Public/private. Manufacturers pay overhead costs of clinical trial; costs of service provision during trial phase will be covered by the SHI funds	Public (by ZonMw; certain budget available but not obligatory) and private ((co)funding by industry or other parties possible)	Both private (manufacturer) or public (NICE or other UK public funders such as NIHR and MRC ^c)	Researchers must find own funding; some studies are government funded; most others are privately supported (e.g. manufacturer)
Decision-making body	Department of Health and Aging	Ministry of Health and Long-Term Care	Ministry of Health	Federal Joint Committee	Ministry of Health, Welfare and Sport	NICE	Centers for Medicare & Medicaid Services
Involved third parties (e.g. academic/scientific institutions, research groups. . .)	MSAC for evidence advise, other partners (e.g. health professionals)	OHTAC/MAS/PATH, THETA, other partners (e.g. academic health science centres, disease specific agencies)	HAS, CNEDiMTS, CEPS, DGS (request and/or assessment of methodology); manufacturers (data collection)	Independent scientific institute, IQWiG assesses eligibility according to potential of benefit	Zorginstituut Nederland, DBC-O, NZa and ZonMw, other partners (e.g. health professionals, academic institutions, manufacturers)	NICE, other partners (health professionals, manufacturers)	AHRQ, MEDCAC, other partners (institutions, health professionals)
Subject of assessment	'Service' is used generically; encompasses clinical procedures, diagnostic tests, medical services and health technologies	Includes medical devices, procedures and other non-drug health technologies ^d	Medical devices and procedures	New diagnostic and therapeutic methods; also methods without a medical device as essential for the new method	'Medical care (incl. specialist drugs ^e)' refers to: care provided by GPs, medical specialists, first line psychologists and obstetricians. Since 1 January also outpatient pharmacy	Devices that have been subject of NICE guidance (either CE marked or adjunct drugs), in-vitro diagnostics that may not have a CE mark, interventional procedures, public health interventions	Surgery, medical devices that might be implanted or used externally, services that occur in physician's office/ambulatory centre, injectable drugs
Topic selection/reasons for applying CED	On a case-by-case basis; if there is inconclusive evidence on safety, effectiveness and cost-effectiveness	Large potential investment, disruptive effects, quality controls desirable prior to unrestricted diffusion, uncertainty regarding safety, low quality of evidence, generalisability	Reducing uncertainty regarding impact, short or long term health outcomes, risk of inappropriate decision and use	Reducing uncertainty about benefit of promising new methods, commercial interest of applicant	New and existing forms of health care; data must be collected on effectiveness and/or cost-effectiveness	Use of new or promising technology/public health intervention; uncertainty about efficacy, safety and cost-effectiveness	Relevance to health outcomes, representativeness of available evidence, re-evaluation of evidence base, generalisability

Table 2 (Continued)

Attributes	Australia	Canada (Ontario)	France	Germany	The Netherlands	UK (England/Wales)	USA
Types of research evidence/study design required	Varies; preference for high quality clinical trials; where suitable well-designed cohort, case-control, comparative and diagnostic studies	Varies according to the nature of the residual uncertainty; (e.g. clinical trials, registry data, prospective observational studies)	Studies have to meet uncertainties raised by the assessment; type depends on the lack of evidence and level of uncertainty; studies with the highest LoE preferred	RCTs preferred (other designs possible in case of e.g. ethical reasons)	Effectiveness requirement is statutorily anchored (e.g. data should be collected on the highest possible LoE).	Varies: any form of study type (e.g. clinical trials, registries, observational studies etc.) that will meet ethical and research governance requirements	RCTs, registries, and prospective cohort studies. The type of study depends on the quality of the existing evidence
Representative examples	PET, TUNA of the prostate, brachytherapy for the treatment of prostate cancer, ...	PET, endovascular abdominal aortic aneurysm repair, drug eluting stents, ...	Extracranial stereotactic radiotherapy, biochemical markers of liver fibrosis, intensity-modulated radiation therapy, ...	Under consideration: PET in three oncologic indications (incl. recurring colon cancer, esophageal cancer, melanoma), ...	Vaccination with autologous, naturally circulating dendritic cells loaded with synthetic peptides in malignant melanoma patients (st IIIb/IIIC, Rituximab maintenance treatment for FL patients responding to first-line induction therapy, ...	MIST wound therapy system, electromechanical gait training for people after stroke, screening for skin cancer, ...	Allo HSCT for the treatment of myelodysplastic syndromes (MDS; artificial heart devices; cochlear implants, ...

Sources: Authors' own compilation based on available information in the public domain (websites), the literature given in the reference list of this article and e-mail exchange with experts from the regulatory institutions and/or organisations involved.

^a Refers to the policy called: Voorwaardelijke toelating.

^b The Canada Health Act establishes the criteria/conditions related to insured health services and extended health care services that provinces/territories must fulfil to qualify for their full share of the federal cash contributions under the Canada Health Transfer.

^c Laboratory tests of devices and retrospective surveys of existing data can be fully-funded by NICE. NICE do not fund clinical trials of devices on patients once recruitment starts, but NICE do facilitate the production of protocols, ethical opinion, peer-review and administration related to research governance. NICE can also recommend that big studies, such as large multicenter RCTs, are funded by UK public funders such as the NIHR and MRC. There is no guarantee that NICE's recommendations for research will be implemented by these funding bodies. Allo HSCT = allogeneic hematopoietic stem cell transplantation; AHRQ = Agency for Healthcare Research and Quality (AHRQ); ASCT = autologous stem cell transplantation; CED = coverage with evidence development; Zorginstituut Nederland = health care insurance board; DBC-O = diagnose behandeling combinatie-onderhoud; DG = diagnostics guidance; FL = follicular lymphoma; GP = general practitioner; HBOT = hyperbaric oxygen treatment; IPG = interventional procedures guidance; IQWiG = Institute for Quality and Efficiency in Healthcare; LoE = level of evidence; MAS = medical advisory secretariat (Ontario); MOHLTC = Ministry of Health and Long-Term Care; MRC = Medical Research Council; MSAC = Medical Services Advisory Committee; MTG = medical technologies guidance; NIHR = National Institute for Health Research; NHS = National Health Service; NHS R&D = NHS Research and Development Forum; NICE = National Institute for Health and Care Excellence; NZa = Nederlandse Zorgautoriteit; OHTAC = Ontario Health Technology Advisory Committee; PATH = Program for the Assessment of Technologies in Health (Ontario); PET = positron emission tomography; st = stadium; THETA = Toronto Health Economics and Technology Assessment Collaborative; TUNA = transurethral needle ablation; Verfo = Verfahrensordnung (rules of procedure); ZonMW = Netherlands organisation for Health Research and Development.

^d Excludes drugs on the Ontario Drug Benefit Program or Information Systems/Information Technology related technologies.

^e Until 2012 mainly expensive inpatient drugs, from January 2013 so called 'specialist drugs'. Conditional entry is not possible for other care forms (e.g. medical devices or oral health care).

processes and methods. As explained in the introduction, CED schemes have the main objective to generate evidence for the finalisation of a coverage decision and to inform future decisions [3,13,32,33]. However, uncertainty about the cost-effectiveness is an additional motivating factor considered specifically in countries like Australia, the UK and The Netherlands, but playing a minor part in other countries including Germany. Nevertheless, all schemes have a strong legal foundation and are anchored in existing legislation, such as the German SGB V. Evidence development in most systems is, at least in parts, funded publicly. However, the share of manufacturers in the funding of studies to a higher degree than in Germany is observable. Contrary to Germany, most countries rely on their Ministry of Health (MoH) (or their equivalent governmental body) as a decision maker in their CED implementation. Only the UK takes an approach similar to that of Germany, by mandating an operationally independent public body – the National Institute for Health and Care Excellence (NICE) – to oversee the British CED scheme [34]. All countries have in common that they rely on additional third parties in any operational steps (e.g. study planning and execution) of their CED schemes.

Turning from the political aspects of CED schemes to their specific scope, we make the following observations. All countries except for The Netherlands, which mainly consider orphans and expensive inpatient pharmaceutical products, focus on non-drug methods including procedures (surgical and non-surgical), diagnostic tests and medical services [35,36]. In addition the UK differs from the remainder of countries because it also considers public health interventions. Furthermore, while Germany solely addresses new diagnostic and therapeutic methods, most countries focus on both existing and new treatment options. The German system is also the only one considering coverage applications for methods not relying mainly on a medical device. No country restricts its CED scheme to a specific indication or condition. Applications range from prevalent to rare and from life threatening to non-life threatening diseases. Finally, we consider the types of study design applicable in the selected systems. Data is gathered either experimentally and prospectively (e.g. RCTs) or under real-life conditions (e.g. registries). While the rules of procedure in Germany mandate RCTs, except if they are not applicable for ethical or other reasons, other countries only state strong preference for evidence from high quality RCTs [7,8,26]. Therefore, there are no clear restrictions regarding the study designs to be used during CED in these cases.

From the above comparison we gather that the selected CED schemes depend on the specific context in which coverage decisions are made in individual healthcare systems. This dependence manifests itself in various details of their implementations. Similar findings have been revealed in previous research [7,13,33]. However, the comparison also exposes the existence of common characteristics among CED schemes, most importantly a clear legislative foundation, a definitive and possibly independent decision-making body, the possibility to obtain public funding for the evaluation, and the preference for high quality study designs. Therefore, despite the differences in

the systems' specifics, these characteristics can be made out as the basis for a developing international standard in CED.

In any case, for a successful CED implementation, one needs to identify the circumstances or technologies suitable for the application of CED in a clear and transparent way, which involves all relevant stakeholders including healthcare providers, decision makers, manufacturers, and patients [3,13]. Experts in- and outside Europe have been focusing on this specific issue in recent years. A relevant example in this context are the results of the 2008 HTAi meeting, summarised by Trueman et al. [6,37]. The summary provides a helpful set of criteria facilitating the identification of technologies suitable for CED *ex ante*. These criteria concern (1) the research problem (e.g. high unmet clinical need or significant improvement in outcomes), (2) the value proposition of a technology (e.g. is the proposition logically and theoretically valid), (3) appropriate data collection (e.g. study design), (4) coverage tool selection (e.g. no coverage tool other than CED is appropriate), (5) primary motivation for the application of CED (e.g. reduction of uncertainty regarding clinical and/or cost-effectiveness, no purely budgetary reasons), (6) time-horizon of the evidence development process (e.g. completion in a timely manner).

The new German regulation on CED meets most of these criteria: Only methods with a clinical need will be considered (criterion 1), methods have to show a potential for medical benefit (2), applicants approach the G-BA in order to generate necessary data that will ultimately lead to a coverage decision (3) because there is not yet sufficient evidence on patient-related benefit (5). Since the German approach to CED is not an alternative to other means of coverage (e.g. risk-sharing agreement), criterion 4 does not apply. The G-BA seeks applications for CED in an early phase of the method life-cycle (6); however, due to process requirements, time could become a critical factor within a CED case. Although these criteria appear to be useful, they still lack empirical validation and should therefore be regarded as a proposal, not as a standard.

5. Conclusion

Experiences with European and international healthcare systems show that controversial decisions for new interventions made under uncertainty may harm patients, may be ineffective, or might cause high economic burdens. Introducing CED policy is a useful step to mitigate these risks by offering preliminary access to promising new technologies while generating the evidence needed to decide whether full coverage of these technologies is warranted. The introduction of the new CED scheme in Germany, through section 137e SGB V, has enabled the G-BA to demand and trigger evidence generation for new diagnostic and therapeutic methods, whilst at least temporarily including these methods in the SHI benefit basket. This change represents a powerful and necessary extension of the previously existing exclusively prohibitive instruments.

Our comparison of this new German legislation with a set of selected international CED schemes demonstrates the dependence of CED implementations on the specifics of the encompassing healthcare system. Nevertheless, we are able to successfully identify a common base of key characteristics in CED such as a clear legislative foundation, a definitive decision-making body, the possibility to obtain public funding, and the preference for high quality study designs, which can be seen as forming an emerging international standard.

Due to the inherent logic of the CED approach, modern healthcare systems should provide this option. The implementation is challenging because of its impact on relevant stakeholders. Therefore it is of particular importance to verify that the use of CED is appropriate under the given circumstances or for specific technologies. The literature has identified six important criteria for this verification. However, despite their usefulness these criteria still need validation and should be further developed. We additionally recommend the introduction of systematic and regular reporting into CEDs. This could be realised for example via reporting systems or registries comparable to registries for clinical trials.

The recent changes in Germany offer an opportunity to observe a new CED scheme in action. The thereby discovered information regarding the benefits and pitfalls of CED policy should find consideration in a continued debate on this issue.

Conflict of interest statement

MP and BO are employed by G-BA.

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